PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference PBM95PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/001574	13.02.2004	

International Patent Classification (IPC) or both national classification and IPC

Applicant
INAZAWA, Johji

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:

   ☐ paid additional fees

   ☐ paid additional fees under protest

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

With regard to the subject matters concerning the respective genes of ABCA3, ABCB6, ABCB8, ABCB10, ABCC4, ABCC9, ABCD3, ABCD4, ABCE1, ABCF2, BCL2L2, BCL2L10, BCL2L1 and BCL2A1 of claims 1-12, a matter common to them is "a method for detecting gene amplification as an indicator of the resistance of a test cancer cell to an anticancer drug."

Reference documents 1-4 (see the following) respectively describe that an ABC transporter gene or BCL2 family gene participates in the resistance of a cancer cell to an anticancer drug and describe a method for detecting the resistance of a cancer cell to an anticancer drug by determining the expression of the ABC transporter gene or BCL2 family gene. So, since the aforesaid common matter is considered to have been publicly known before the filing date of the present application, the said common matter belongs to the prior art and is not the special technical matter referred to in PCT Rule 13.2.

Therefore, the subject matters of claims 1-12 of the present application are not considered to be a group of subject matters so linked as to form a single general inventive concept.

Reference document 1: WO, 02-28894, A1
Reference document 2: Cancer Research, 2001, Vol. 61, pages 2827-2832
Reference document 3: American Journal of Clinical Pathology, 2000, Vol. 113, pages 219-229
Reference document 4: Oncogene, 2001, Vol. 20, No. 11, pages 1300-1306

So, the International Searching Authority considers that claims 1-12 of the present application include 14 inventions in total relating to the respective genes of ABCA3, ABCB6, ABCB8, ABCB10, ABCC4, ABCC9, ABCD3, ABCD4, ABCE1, ABCF2, BCL2L2, BCL2L10, BCL2L1 and BCL2A1.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-12 (only the portions relating to ABCA3)

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8, 10	YES
	Claims	9, 11, 12	NO
Inventive step (IS)	Claims	2	YES
	Claims	1, 3-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations:

Document 1: Int. J. Cancer, 10 January, 2004 (10.01.04), Vol. 108, No. 2, pages 212-218
Document 2: FEBS Lett., 1996, Vol. 391 (1-2), pages 61-65
Document 3: Curr. Mol. Med., 2001, Vol. 1, No. 1, pages 45-65
Document 4: Oncogene, 2001, Vol. 20, pages 1300-1306
Document 5: Cancer Res., 1999, Vol. 59, No. 23, pages 5964-5967

Document 1 describes to the effect that (1) a DNA immobilized substrate was prepared from a promyeloic leukemia cell for observing the change of gene expression caused by administering cantharidin to the said cell, and (2) the expression of ABCA3 gene decreased (see Table 1). The document (page 216, right column, lines 25-40) further describes to the effect that (1) a cancer cell overexpressing a so-called multiple drug resistant gene shows resistance to a wide range of drugs and (2) above all, the change in the expression of an ABC transporter gene participates in the said resistance and also to the effect that the decline in the expression of ABCA3 gene caused by the administration of cantharidin is consistent with the enhancement of susceptibility of cancer cells to drugs.

Document 2 describes that a human ABC-C gene was cloned, and suggests that since the said gene is a member of ABC transporter family, it has relation with the chemotherapeutic drug resistance of cancer.

Document 3 describes that an ABC transporter family gene participates in the drug resistance of cancer cells, and also describes a method for determining the expression of the said gene.

Document 4 (page 1300, the paragraph of Introduction) describes to the effect that the overexpression of ABCB1 gene participates in the emergence of multiple drug resistant cancer cells.

Document 5 describes to the effect that when MRP3, one of ABC transporters, was highly expressed in a cell, the resistance to etoposide rose to about 4 times.
Respective claims

Since the cDNAs of ABCA3 gene and a DNA synthesis gene exist on the DNA immobilized substrate described in document 1, the subject matters of claims 9, 11 and 12 of the present application are equivalent to the invention described in document 1 and do not appear to be novel.

Based on the description of document 1, ABCA3 gene belongs to the ABC transporter family and deeply participates in multiple drug resistant cancer cells. So, a person skilled in the art

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

could have easily observed the change in the expression of the said gene in a cancer cell using, for example, a DNA chip, to detect the acquisition of drug resistance. Therefore, the subject matters of claims 1, 3-5, 7 and 8 of the present application do not appear to involve an inventive step, since a person skilled in the art could have easily arrived at them from the invention described in document 1.

The ABC-C gene described in document 2 is no more than ABCA3 gene, and since it is well known that the expression of an ABC transporter gene has relation with drug resistance as described in document 3, a person skilled in the art could have easily conceived of placing the cDNA of ABCA3 on, for example, a DNA chip and determining the expression in a cancer cell, for detecting whether or not drug resistance has been acquired. Furthermore, a person skilled in the art could have, as required, placed, for example, ABCB1 gene belonging to the same ABC transporter and known to relate to drug resistance (see document 4) simultaneously together with ABCA3 on a DNA chip for detection. Therefore, the subject matters of claims 1 and 3-12 of the present application do not appear to involve an inventive step, since a person skilled in the art could have easily arrived at them from the inventions described in documents 2-4.

Documents 1-5 neither describe nor suggest the correlation between the expression of ABCA3 gene and the drug resistance to etoposides. Furthermore, a person skilled in the art could not have predicted that the expression of ABCA3 gene in HT-29/ETP cell, a carcinoma of the colon and rectum resistant against etoposide, is significantly higher than that in the control parent strain cell.

Therefore, the subject matter of claim 2 of the present application appears to be novel, to involve an inventive step and to be industrially applicable.